Neuroworsening in Moderate Traumatic Brain Injury

Daniel Agustin Godoy, MD[a], Francesca Fossi, MD[b], Chiara Robba, MD, PhD[c,d,*]

KEYWORDS

• Traumatic brain injury • Outcome • Neuroworsening • Intensive care unit

KEY POINTS

- Neuroworsening (NW) is a potentially lethal complication of moderate traumatic brain injury (MoTBI).
- The causes and risk factors of NW should be promptly identified.
- Intensive care unit should be considered whenever there are risk factors of NW.
- NW requires prompt and aggressive therapeutic approach.
- Outcome is deeply affected by NW.

INTRODUCTION

Traumatic brain injury (TBI) is still a leading cause of mortality and disability worldwide.[1,2] Despite its high prevalence, little attention has been paid to the management of moderate TBI (MoTBI), as the majority of evidence has been focused on more severe cases. The relatively limited information available explains the lack of specific guidelines.[3]

Patients with MoTBI represent 20% of all TBI admissions to the emergency department.[3,4] According to current literature, these patients are poorly defined and categorized, and there are still many unanswered questions regarding their management; in fact, MoTBI falls into a "gray area,"[3] where monitoring, neuroimaging, and therapeutic strategies are not well established.

[a] Neurointensive Care Unit, Sanatorio Pasteur Medical Center, Catamarca, Argentina; [b] Neurointensive Care Unit, Grande Ospedale Metropolitano Niguarda, Milano, Italy; [c] Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Italy; [d] Neurological and General Intensive Care, IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi, 10, Genova 16100, Italy

* Corresponding author. Neurological and General Intensive Care, IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi, 10, Genova 16100, Italy.
E-mail address: kiarobba@gmail.com

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Classically, patients with Glasgow Coma Scale (GCS) score ranging from 9 to 12 points postresuscitation are categorized as "moderate."[2] However, a recent consensus[4] recommended—based on available evidence—to include a score of 13 points of GCS in the moderate group.[5–7]

The epidemiologic profile of MoTBI may change according to age and available resources.[8] In low-income countries, for instance, MoTBI is mainly observed in young people following traffic accidents or violence and is frequently accompanied by extracranial injuries; meanwhile, in high-income countries, MoTBI is mainly observed in the elderly population (who have more comorbidities and are often taking multiple pharmacologic agents, including anticoagulants) and, in general, caused by purely cranial trauma due to low-energy impacts.[8]

TBI is a dynamic and heterogeneous entity.[1,2] Cases classified as "moderate" do not escape this assertion and can show a wide variety of clinical pictures and lesional spectrum.[3] Yet, a simple way to remember the presentation and evolution of patients with MoTBI is that about 30% will present intracranial injuries, 30% will require a surgical procedure, and 30% will present a clinical deterioration (rule of 30).[3]

MoTBI is a serious entity.[3] More than half of the individuals who suffered MoTBI will present long-term neurocognitive sequelae, many of which will be permanent and will prevent social reintegration or resumption of life prior to the trauma.[3] Furthermore, the mortality of MoTBI is not negligible, averaging around 15%.[3]

Neuroworsening (NW) is a feared complication after MoTBI.[4,9,10] NW can manifest in various ways[4,9] and may occur in different evaluative periods after trauma.[9] Multiple predisposing factors for NW have been described; however, so far, there is no validated predictive model[4,9] to guide clinicians in the early detection of patients at risk. This is a crucial point, as NW is associated with poor prognosis.[4,9,10]

Therefore, NW is a medical-surgical emergency that requires the adoption of specific protocols for its prevention, prompt detection, and aggressive management.[4,9]

NEUROWORSENING: WHAT ARE WE TALKING ABOUT?

Deterioration of neurologic status, neurologic decline, neurodeterioration, and NW are generally considered synonyms. There is currently no widely and universally validated definition for the term "NW" in MoTBI and the existing ones have been extrapolated from the severe TBI population.[4,9,11] There are different ways to define NW.[4]

Clinical Neuroworsening

Classically, NW has been described on a clinical basis as a decline in neurologic examination.

The first definitions of NW were developed as outcome measures in pharmacologic trials that included patients with moderate and severe TBI.[11,12] The criteria necessary for its definition were mainly objective (decreased of 2 or more points in the motor component of GCS (mGCS), loss of pupillary reactivity or new pupillary asymmetry [2 mm or greater]), although some others were subjective and often unclear, such as "*any deterioration in neurologic status.*"[11,12]

A New Zealand study employed a similar definition of NW after MoTBI, but the authors considered a decrease in total GCS punctuation rather than the motor component.[13] More recently, the Best Trip trial, which used a clinical and imaging protocol to manage intracranial hypertension in severe TBI, utilized the following criteria for NW[14]: (1) decrease in the mGCS greater than 2 points; (2) a new loss of pupillary reactivity; (3) interval development of pupillary asymmetry greater than 2 mm; (4) new focal motor deficit, and (5) herniation syndrome. Subsequently, consensus revised ice (CREVICE)

protocol[15] and the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC)[16] consensus defined NW in a similar manner with the exception of changing the decrease in mGCS to greater than 1 point and/or the presence of seizures. Observational studies on MoTBI have used this same definition.[17–20] Recently, the Latin American consensus on MoTBI suggested to add worsening headaches and increased intensity and frequency of vomiting to the clinical criteria to define NW in individuals who are not sedated or intubated.[4]

When analyzing the clinical criteria, it is important to consider limitations due to the need of using sedation, analgesia, and neuromuscular blockade, which can preclude examination or mask the clinical picture.

Radiological Neuroworsening

Neuroimaging, especially computed tomographic (CT) scan, is an essential tool in the management of MoTBI. In the context of MoTBI, CT scan allows the assessment of the type and extension of the lesion, its location and need for neurosurgical interventions.[21–23] Additionally, it provides important pathophysiological and prognostic information, playing an important role in the follow-up and in therapeutic decision-making.[21]

In the early 1990s, Marshall and colleagues[24] developed a tomographic scale based mainly on the presence and volume of the space-occupying lesion, the basal cisterns status, and the presence of midline shift. Additionally, this scale takes in consideration whether the hemorrhagic collections have been surgically evacuated or not.[24]

The Marshall scale has been widely validated in neurotrauma units around the world due to its predictive capacity to establish intracranial hypertension and the final outcome,[25–28] and its use has been widely extended from a research field to daily clinical practice.[25] When estimating prognosis, the controversy still persists as to whether it is optimal to use the CT on admission or the one considered “worst” in subsequent follow-up.[29]

Subsequently Maas and colleagues[30] in Rotterdam developed a predictive model based on CT scan parameters obtained from logistic regression analysis, which included basal cisterns status, midline shift, and the presence or absence of intraventricular bleeding (intraventricular hemorrhage [IVH]), subarachnoid hemorrhage (SAH), and epidural hematoma. This ordinal model is more discriminative and has been shown to have better predictive value for outcome when compared to the Marshall score; however, it is still not widely used in clinical practice.[31,32]

Neuroimaging has a key role in diagnosis of NW.[4] The progression or presence of new lesions on follow-up CT scan is an NW definition by itself.[4,9] Radiological worsening may anticipate or present simultaneously with clinical worsening.[4,9] As a general rule, a deterioration in CT scan even without changes in neurologic examination must be a warning signal for closer monitoring.

The criteria employed to define radiological NW (**Fig. 1**) are[4,9]

- New space-occupying lesion.
- Increase in volume of previous lesion.
- New onset or increase in volume of cerebral edema.
- Basal cisterns compressed or absent (new onset or worsening of previous one).
- Midline shift increase.

According to the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot study in mild TBI, subjects with early NW showed a higher lesional burden in initial CT scan.[33] The most common associated injuries were subdural hematoma (SDH), SAH, cerebral contusions, and IVH.[33] Early NW was also

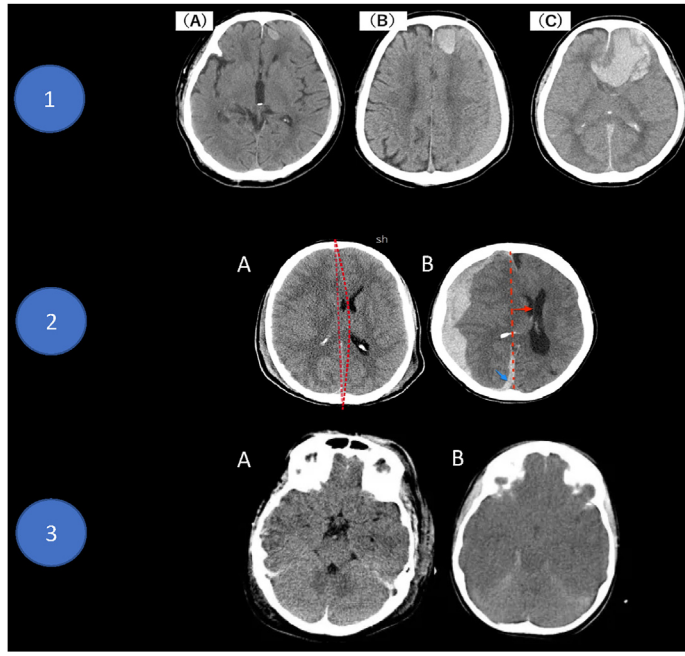

Fig. 1. Radiological NW criteria. (1) Cerebral Contusion. Progression of primary injury. (A) Admission; (B) 5 hours, and (C) 24 hours after admission. (2) Midline shift increase. (A) 4 hours after trauma, (B) 12 hours after trauma after clinical deterioration (decrease 2 points in motor GCS). (3) Basal Cisterns obliteration. (A) 1 hour after TBI and (B) 14 hours after admission.

associated with signs of high intracranial pressure (ICP) such as midline shift (50%), cisternal compression (56%), and cerebral edema (69%).[33]

Neuroworsening Detected by Cerebral Monitoring

The pathophysiology of MoTBI does not differ in any way than in severe TBI.[3] After the trauma and according to its kinetics, a series of lesions that constitute the "primary injury" develop macroscopically and microscopically.[2,3,25,26]

Simultaneously and consecutively, a series of intracranial phenomena and cascades (inflammation, coagulation, endocrine, and metabolic) are triggered and, depending on the type, magnitude, and severity of the initial damage, will contribute to the development of different forms of secondary injury, among which intracranial hypertension, cerebral tissue hypoxia, metabolic crises, and cerebral energy dysfunction are the most common and dangerous.[2,3,25,26]

Over the last years, the development of new monitoring techniques (invasive and noninvasive) have allowed, through the information obtained, the integration and deep analysis in real time of pathophysiological changes occurring in the injured brain.[1,25,26,34,35]

A recent systematic review and metanalysis of patients with MoTBI showed that invasive ICP monitoring was used in 18.3% (95% confidence interval [CI]: 8.1%–36.1%) of cases, and intracranial hypertension was documented in 44% (95% CI: 33.8%–54.7%) of monitored patients.[36] ICP monitoring was performed in 32.2% of patients with a GCS of 10 or less versus 15.2% of patients with GCS greater than

10 ($P = .59$).[36] However, the studies included in the systematic review were highly heterogeneous and the risk of bias was high. No variables associated with use of ICP monitoring or detection of intracranial hypertension were found.[36] At present, there are no studies regarding the use of invasive cerebral oxygenation monitoring in patients with MoTBI.

Noninvasive neuromonitoring are promising tools that can help in the categorization and follow-up of patients with MoTBI and can potentially add important information to prevent and diagnose NW. Several techniques are available and others are in development. Measurements of the optic nerve sheath diameter (ONSD) using ultrasound correlate with an increased ICP, particularly when using a threshold of ONSD greater than 6 mm.[37]

Recently, a technique based on the detection of microexpansions of the cranial vault was shown to be able to reliably display the morphology of the ICP wave; the relationship between the P1 and P2 components and the time for the peak of the wave had good correlation with invasive ICP values.[38,39] Although it is a developing technique, growing evidence is promising.[38,39] Because this modality is exquisitely sensitive to motion, it is only reliable in sedated (and ideally paralyzed) patients.

Bouzat and colleagues[40] studied the role of transcranial Doppler (TCD) in the prediction of NW and outcome of mild and MoTBI. Normal TCD was considered when values of pulsatility index were less than 1.25 and diastolic blood flow velocity was higher than 25 cm/s in both middle cerebral arteries.[40] In this study, 6% of 356 patients developed NW,[40] and TCD had 80% sensitivity (95% CI: 56%–94%) and 79% specificity (95% CI: 74%–83%) to predict NW.[40]

The American Nurse Association recently published a prospective observational study in patients with TBI evaluating the correlation between NW (defined as deterioration of 2 or more points in total sum of GCS) and Neurologic Pupil index (NPi) measured by quantitative pupillometry in the first 24 hours after admission.[41] There was a significant association between NPi less than 3 and NW ($P < .0001$).[41] The sensitivity of the NPi to detect NW was 51.4% and the specificity was 91.7%.[41]

In summary, in individuals monitored either invasively or noninvasively, alterations in neuromonitoring parameters may denote a deterioration in the clinical condition, which should trigger the necessary measures to detect and correct the possible cause(s) that originate it. The Latin American consensus of MoTBI suggests the following criteria of NW in the variables obtained from monitoring[4]:

- Pulsatility index in TCD greater than 1.4
- ONSD greater than 5 mm
- Pupillometry (NPI <3)
- Change ICP waveform (P2 > o = P1) invasive or noninvasive
- ICP greater than 22 mm Hg
- $PbtO_2$ less than 20 mm Hg
- $SjVO_2$ less than 50%
- Noninvasive cerebral oxygenation near infrared spectroscopy (NIRS) < than 50%
- Epileptic discharges in electroencephalogram monitoring

Integrative Definition of Neuroworsening

Integrating the above criteria, the Latin American consensus proposes the following definition[4]:

In MoTBI, NW is defined as "*the deterioration in 1 or more of the following* baseline characteristics: clinical, imaging, or neuromonitoring status (invasive or noninvasive), sufficient to require medical or surgical therapy."

CAUSES AND TIMING OF NEUROWORSENING AFTER MODERATE TRAUMATIC BRAIN INJURY

NW can appear at any time during the evolution of the TBI. The literature describes 2 main periods for deterioration, "early or late," depending on whether it occurs before or after 72 hours after injury.[9,11,17]

In general, the causes of NW follow specific pathophysiological changes. Basically, we can identify 3 principal events.

a. *Progression of the primary injury* (SDH, extradural hemorrhage [EDH], and contusions). In 1975, a group of individuals (most of them with epidural hematomas) was described under the acronym "talk and died," characterized by initially presenting a score in the verbal component of the GCS of 3 or more points, but who subsequently deteriorated and died, generally due to potentially reversible causes.[42] Most of these patients belonged to the "moderate" group.[43–48] Increase in size of cerebral contusions is an important risk factor for NW within the first 1 to 2 days after trauma.[49]
b. *Secondary insults*, which may originate following intracranial complications (intracranial hypertension, tissue hypoxia, cerebral edema, appearance of new lesions, seizures, sympathetic hyperactivity, vasospasm, spreading depression, and hydrocephalus) or extracranial causes (arterial hypotension, hypoxemia, hypercapnia, intrathoracic or intra-abdominal hypertension, hypoglycemia, hypocapnia, and hyperthermia).[9,11]
c. *Iatrogenic*, which include adverse effects from drugs (sedatives, analgesics, osmotherapy agents, and vasopressors), complications of mechanical ventilation (inadequate ventilation or high intrathoracic pressures and oxygen toxicity), and sepsis (vascular catheters, neuromonitoring devices, and pneumonia).[9]

Another way to categorize the causes of NW is according to their origin. Neurologic and nonneurological causes can be recognized. In MoTBI, neurologic causes are more frequent in the "early" period, mainly driven by the appearance of new intracranial lesions or to the progression of mass effect.[9,11–13]

HOW OFTEN DOES NEUROWORSENING OCCUR IN MODERATE TRAUMATIC BRAIN INJURY?

The prevalence of NW after MoTBI is far from negligible, estimated at 1 every 4 patients. Analyzed series have showed a prevalence that ranges between 12% and 49.6%, averaging 28%.[12,13,17–19,50,51]

RISK FACTORS FOR NEUROWORSENING IN MODERATE TRAUMATIC BRAIN INJURY

In MoTBI, the available literature is scarce and present multiple and varied methodological limitations. Chen and colleagues[18] in a Chinese retrospective series that included 479 patients with MoTBI studied different clinical, radiological, and laboratory parameters evaluated at hospital admission as potential predictors of NW. In the multivariate logistic regression analysis, the following factors were found to be associated with worse outcome[18]: presence of arterial hypertension; Marshall's CT scale types III and IV; SDH, frontal and temporal contusions, Injury Severity Score greater than 13, D-dimer level greater than 11.4 mg/L, GCS less than 10 points, and platelet count less than 152,000/mm^3.

Based on these findings, the aforementioned group created a prediction model, which is presented in a nomogram.[18] The prediction model was first internally

validated and showed that the C-statistic of the prediction model was 0.881 (95% CI: 0.849–0.909). External validation showed that the nomogram could predict NW with an area under the curve (AUC) of 0.827 (95% CI: 0.763–0.880).[18]

A Latin American series that included 232 individuals (Godoy DA, data not yet published, 2024) identified in the multivariate analysis the following risk factors associated with NW: GCS (odds ratio [OR]: 0.50; 95% CI: 0.28–0.96), Marshall CT score (OR: 2.34; 95% CI: 1.25–4.35), contusions (OR: 3.06; 95% CI: 1.53–20.07), temporal location of the contusion (OR: 3.61; 95% CI: 1.39–9.67), presence of multiple contusions (OR: 2.79; 95% CI: 1.33–5.82), and extracranial injuries (OR: 2.79; 95% CI: 1.33–5.82). With these parameters, the authors developed a score that showed 85% accuracy. However, this prediction model needs external validation.

Other NW risk factors described in literature include age greater than 65 years; heart rate, mean arterial pressure, and temperature variability (based on activation of sympathetic system); and infections and coagulopathy.[33,52]

Godoy and colleagues[10,53] proposed a simple and practical way to categorize risk groups in MoTBI, including GCS and Marshall CT scale into the so-called traffic light method. According to this method, when the score in the Marshall scale is III or IV and the GCS is below 11, the risk of NW increases ("red light") and the patient should undergo strict neuromonitoring in the intensive care unit (ICU).[10,53]

DO BIOMARKERS HAVE A ROLE IN NEUROWORSENING PREDICTION?

Biomarkers (BMs) are molecules that reflect important pathophysiological processes.[54–56] After TBI, proteomic BMs are secreted into the circulatory system.[57] BMs can be an auxiliary tool to categorize the severity and the risk of TBI progression.[54–56] BMs have demonstrated to have good ability to predict outcome[54–56] and can be useful as noninvasive neuromonitoring tools.[58] Many of these markers are specific to neuronal cells, and others to glia or axons, reflecting damage to different components of the brain parenchyma.[54–56] Some BMs reflect blood–brain barrier damage or inflammation.[54–56] S 100 beta protein, neuron-specific enolase, glial fibrillary acid protein (GFAP), and ubiquitin C-terminal hydrolase-L1 (UCH-L1) are the most commonly investigated BMs.[59,60] Recently, neurofilament light chain (NFL), an intermediate filament protein abundantly expressed in subcortical axons, has been studied as a prognostic biomarker in TBI.[61]

The initial levels and temporal profile of a panel of BMs can characterize the severity of brain damage.[60] In a CENTER-TBI study, Whitehouse and colleagues[62] showed that BM concentrations are associated with lesional burden: parenchymal injuries have higher concentrations than extraparenchymal injuries. UCH-L1 primarily increases in diffuse injury, while GFAP shows higher levels in focal mass lesions.[63] Interestingly, some BMs are elevated despite normal CT scan.[62] GFAP and UCH-L1 appear to be elevated in patients with MoTBI without CT scan findings but with evidence of injury on MRI.[64] These BMs might be elevated in occult neurologic injuries such as patients with persistent postconcussion syndrome and negative neuroimaging.[62] TAU and NFL are promising BMs to assess the severity of diffuse axonal injury.[62] Also, BMs of systemic metabolic stress are consistently associated with worse prognosis, compared to patients with normal metabolic profile.[65]

Yet, some important open questions remain to be elucidated before BM can be recommended for use in daily clinical practice, such as (1) is the optimal set of BM? (2) Is it necessary to measure BM in cerebrospinal fluid or is it sufficient measuring them in serum? (3) Which is the kinetics of BMs (production, elimination, and half-life); and

(4) which is the most appropriate timing for initial and following sampling of BMs.[1–3,8] Additionally, the accuracy of BMs for prediction of long-term outcomes and their association with the severity of the injury are only modest at present.[54,56,66]

Despite these uncertainties, BMs have a huge potential for recognizing the risk of NW at an early stage, and thus guide the use of neuromonitoring. We think that BM will be soon incorporated into the decision-making algorithm for patients with MoTBI.[66]

WHAT IS THE IMPACT OF NEUROWORSENING ON THE OUTCOME OF PATIENTS WITH TRAUMATIC BRAIN INJURY?

NW has a profound negative impact on patients' outcome and has been associated with greater mortality and high burden of moderate and severe neurologic disability after severe TBI.[11,12] The Selfotel and Tirilazad trials demonstrated that mortality and poor outcomes (evaluated as glasgow outcome score GOS] at 6 months) were clearly higher among patients who had NW ($P < .001$).[11,12] Compagnone and colleagues[17] also found higher risk of poor clinical outcomes in patients with NW (OR: 3.24; 95% CI: 1.65–6.39; $P = .0004$). Similar findings were noted in other cohorts, where NW was independently associated with death or severe disability.[50,67]

According to TRACK-TBI study, individuals with NW showed higher in-hospital mortality (37.5% vs 0.6%; $P < .001$) and unfavorable 3 and 6 month outcomes (58.3%/4.9%; 53.8%/6.2%; all $P < .001$)[33] compared to those who did not have NW.

HOW TO APPROACH PATIENTS WITH NEUROWORSENING?

NW is often a neurologic and neurosurgical emergency.[4,9] Therefore, clinicians have to pay close attention to diagnose NW early and treat its possible causes.[3,4,9,10]

The recent Latin-American MoTBI consensus suggests the institutional development of surveillance, detection, and early action protocols for NW.[4]

In many hospitals, patients with MoTBI are not routinely admitted to the ICU.[4] If the neurologic examination, initial CT scan and vital signs are normal, usually these patients are managed in the first hours (or even days) in the emergency department. However, during this window of time, the patient may deteriorate. Noninvasive neuromonitoring can be helpful to follow up this group of patients.[4]

The alarm level should never be lowered. Management hinges on serial clinical examination and achieving physiologic homeostasis, avoiding secondary insults of systemic origin.[4] It is important to ensure the ABCs of trauma, evaluating and taking the necessary measures to maintain adequate airway, ventilation, and systemic oxygenation,[3,4] to avoid arterial hypotension, hypoglycemia, and correct any abnormal physiologic parameters.[3,4,68]

In agitated patients who require sedation after adopting nonpharmacological measures, we recommend a "cooperative" regimen that avoids obscuring the clinical neurologic examination while maintaining cardiorespiratory stability.[69]

The optimal strategy for radiological monitoring is unclear.[4] Recent consensus suggests performing a follow-up scan at 6 to 8 hours if the patient is admitted within 6 hours of the trauma.[4] Subsequently, a new CT is recommended at 24 hours after admission if the patient does not develop NW.[4]

It is also crucial to appropriately triage patients who necessitate ICU admission because of high risk of NW. In this context, the traffic light method is an easy, simple, and practical tool to categorize the risk.[10] In general, patients with MoTBI with positive CT scan should be admitted to ICU[3,4,10,70] in order to receive a more intensive neuromonitoring assessment.[4]

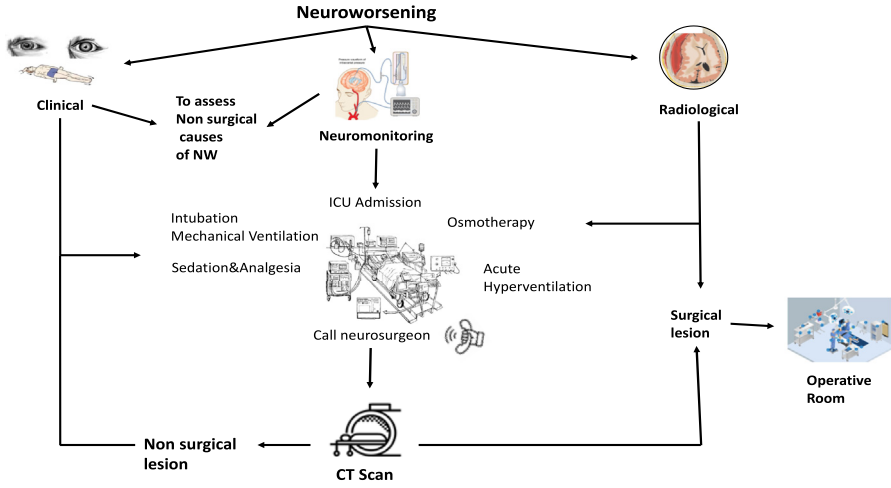

Fig. 2. NW approach. CT, computed tomography; ICU, intensive care unit; NW, neuroworsening.

The management of NW should be directed toward the determination of the cause, the treatment of intracranial hypertension, and neurosurgical intervention if needed based on imaging findings.[15,16] Intubation, mechanical ventilation, sedation and analgesia, osmotherapy, and hyperventilation should be considered in the acute phase.[16] If surgical lesion is excluded, invasive neuromonitoring may be useful[15,16] (**Fig. 2**).

SUMMARY

Patients with MoTBI are a high-risk group for the development of NW, and therefore, it is key to properly categorize them. Although a standardized and validated definition of NW is not available, NW can be defined in several ways (clinical, radiological, by invasive or noninvasive neuromonitoring) and generally denotes progression of the primary insult or occurrence of secondary intracranial or extracranial insults. It can occur at any time during the evolution of TBI. The most consistent risk factors are GCS and the type of injury detected on the CT scan. NW is not an uncommon complication of MoTBI, and its consequences are often devastating. Thus, it is imperative to develop surveillance, detection, and early management protocols to mitigate the effects of NW on the outcome of patients with TBI.

CLINICS CARE POINTS

- Patients with moderate Traumatic brain injury are at high risk of Neuroworsening.
- Literature is heterogeneous regarding the definition and the monitoring/treatment strategies of this population.
- Clinical examination and neuroimaging are fundamental to assess the risk of neuroworsening together with neuromonitoring and biomarkers.
- Research is warranted to provide evidence on the risk factors and predictors of Neuroworsening in moderate Traumetic brain injured patients.

DISCLOSURE

All authors declare that they have neither commercial nor financial conflicts of interest.

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